Palladium-Catalyzed Cross-couplings of Lithium Arylzincates with Aromatic Halides. Synthesis of Analogues of Isomeridianin G and Evaluation as GSK-3 Inhibitors

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Anne Seggio,[a,b] Ghislaine Priem,[b] Floris Chevallier,[a] and Florence Mongin*[a]

[a] Chimie et Photonique Moléculaires, UMR CNRS 6510, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes Cedex, France.

[b] GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow CM19 5AW, United Kingdom.

Fax: (+33)2-2323-6955; E-mail: florence.mongin@univ-rennes1.fr

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Abstract: Several analogues of Isomeridianin G have been synthesized using as a key step palladium-catalyzed cross-coupling reactions of lithium triorganozincates. The latter have been prepared by deprotonative lithiation followed by transmetalation using $ZnCl_2$·TMEDA (1/3 equiv).

Key words: Cross-coupling, Heterocycles, Palladium, Zinc, Lithium.

The importance of heterobiaryls in compounds of biological interest have stimulated tremendous efforts for the development of synthetic methods in the area of aryl-aryl bond formation.[1] Like the Suzuki-Miyaura[2] and Stille[3] reactions, the Negishi[4] cross-couplings between organozincs and aryl halides are known to tolerate numerous functional groups. When compared with the first reactions, the latter become attractive when heteroaryl boronic acids cannot be prepared, furthermore they do not require highly toxic starting materials.

The organozincs are often prepared by reacting the corresponding lithium or magnesium compounds with zinc halides.[5] A drawback of the Negishi coupling procedure lies in the fact that dry zinc chloride or zinc bromide is required.

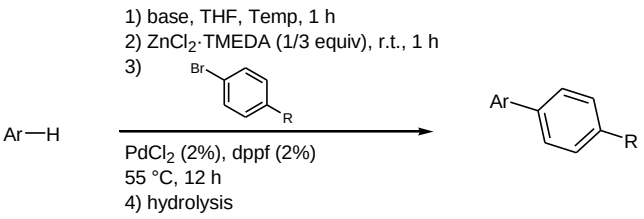
Miller and Farrell reported the use of a catalytic amount of zinc chloride to perform nickel- or palladium-catalyzed couplings of aryl Grignard reagents with aryl halides.[6] Other studies avoided the use of a zinc salt by generating lithium zincates either by iodine-metal exchange[7] or by deprotonation.[8] In 2002, Gauthier and co-workers documented an approach through lithium zincates using only one third equivalent of zinc chloride for the synthesis of 5-aryl-2-furaldehydes from 5-lithio-2-furaldehyde diethyl acetal.[9] In addition, Mutule and Suma described in 2005 one pot Grignard formation-transmetalation-Negishi reactions using the less hygroscopic TMEDA-chelated zinc chloride.[10]

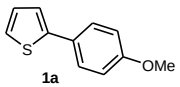
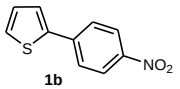
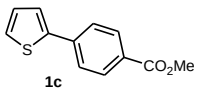
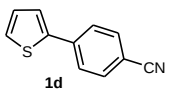
We have recently published palladium-catalyzed Negishi reactions[11] for which the lithium triarylzincates were generated by transmetalation of the corresponding lithio compounds using $ZnCl_2$·TMEDA.[12] Herein, we report the whole study, as well as the use of the deprotonation-transmetalation-coupling sequence as a key step for the synthesis of molecules of biological interest.

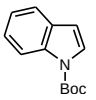
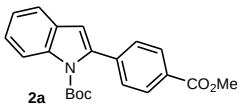
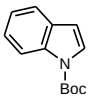
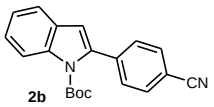
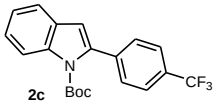
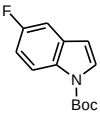
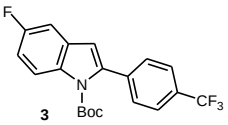
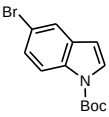
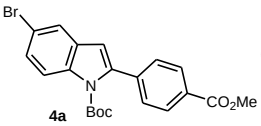
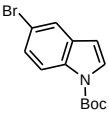
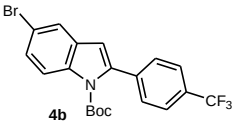
For this present study, numerous lithio aromatics obtained by deprotonation were transmetalated using 1/3 equivalent of $ZnCl_2$·TMEDA. The lithium triarylzincates generated were then involved in cross-coupling reactions with aromatic halides using catalytic amounts of palladium(II) chloride and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (2 mol.% each).[13]

Diverse 4-substituted bromobenzenes[14] were used (Table 1). Thiophene was lithiated using butyllithium in tetrahydrofuran (THF) at –75 °C,[15] before the transmetalation step to generate lithium tri(2-thienyl)zincate. The subsequent palladium-catalyzed cross-coupling was performed with 4-bromoanisole, 4-bromonitrobenzene, methyl 4-bromobenzoate and 4-bromobenzonitrile at 55 °C to afford the corresponding derivatives **1a-d** in yields ranging from 10[16] to 79% (entries 1-4). It was noticed that reactions performed with the corresponding chlorobenzenes, which have higher carbon-halogen bond dissociation energies,[17] failed. *N*-Boc indole was deprotonated upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at –90 °C,[18,19] and then treated similarly to provide the expected substituted *N*-Boc 2-phenylindoles **2a-c** (entries 5-7). These conditions also proved suitable for the functionalization of 5-fluoro and 5-bromo *N*-Boc indoles (compounds **3**, **4a-b**, entries 8-10).

Table 1 Coupling Reactions of Lithium Triarylzincates with Substituted Phenyl Bromides



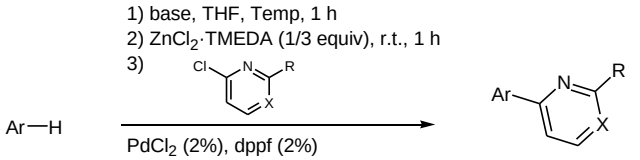
Entry	Substrate	Base, Temp	Product	Yield
1		BuLi, –75 °C	 **1a**	10%
2		BuLi, –75 °C	 **1b**	38% 76%[a]
3		BuLi, –75 °C	 **1c**	41%
4		BuLi, –75 °C	 **1d**	79%

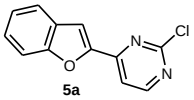
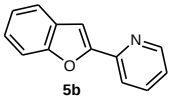
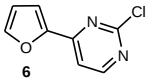
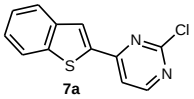
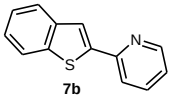
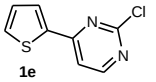
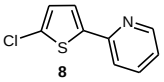
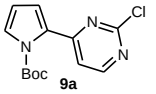
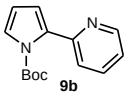
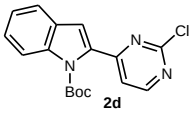
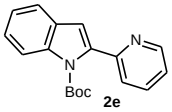
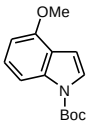
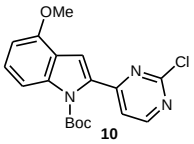
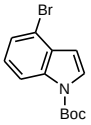
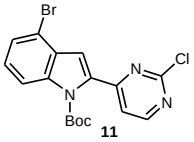
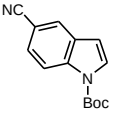
5		LiTMP, –90 °C	 **2a**	48%
6		LiTMP, –90 °C	 **2b**	61%
7		LiTMP, –90 °C	 **2c**	60%
8		LiTMP, –90 °C	 **3**	36%
9		LiTMP, –90 °C	 **4a**	66%
10		LiTMP, –90 °C	 **4b**	31%

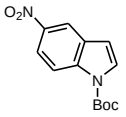
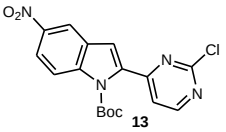
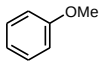
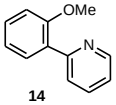
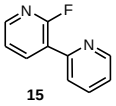
[a] Coupling step performed in presence of DME (5 equiv).[14g]

Activated heteroaryl chlorides[20] were also used to prepare bis(heterocycles) (Table 2). The 2-lithio benzo[*b*]furan derivative was prepared using butyllithium in THF at –15 °C,[21] and converted to the corresponding lithium arylzincate. Subsequent cross-coupling with 2,4-dichloropyrimidine and 2-chloropyridine provided the expected bis(heterocycles) **5a**,**b** in satisfying yields (entries 1,2).[22,23] The furylpyrimidine **6** was prepared similarly (entry 3).[24] Benzo[*b*]thiophene, thiophene and 2-chlorothiophene were deprotonated using butyllithium at –75 °C,[15] and the lithio derivatives gave the corresponding coupled products **7a**-**b**, **1e** and **8** (entries 4-7). *N*-Boc pyrrole was deprotonated upon treatment with LiTMP in THF at –75 °C[25] to give the pyridyl and pyrimidyl derivatives **9a**-**b** after subsequent transmetalation-coupling reactions (entries 8,9). The syntheses of the 2-indolyl-pyridine **2e** and -pyrimidines **2d**,**10**-**13** were performed from different 2-lithiated *N*-Boc indoles generated by deprotonation using LiTMP at –90 °C (entries 10-15). Anisole was similarly *ortho*-functionalized after direct lithiation at 25 °C[26] to afford the 2-pyridyl derivative **14** (entry 16). The reaction also proved convenient for the functionalization of a π-deficient substrate, 2-fluoropyridine, which was converted to the unsymmetrical bipyridine **15** (entry 10) after lithiation using LiTMP in THF at –75 °C,[27] followed by transmetalation and cross-coupling steps.

Table 2 Coupling Reactions of Lithium Triarylzincates with Heteroaryl Chlorides

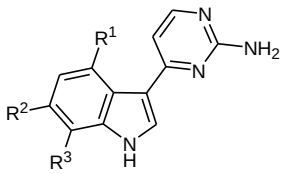


Entry	Substrate	Base, Temp	Product	Yield
1		BuLi, –15 °C	 **5a**	56%
2		BuLi, –15 °C	 **5b**	61% 76%[a]
3		BuLi, –15 °C	 **6**	61%
4		BuLi, –75 °C	 **7a**	29%[b]
5		BuLi, –75 °C	 **7b**	81%
6		BuLi, –75 °C	 **1e**	56%
7		BuLi, –75 °C	 **8**	85%
8		LiTMP, –75 °C	 **9a**	25%[b]
9		LiTMP, –75 °C	 **9b**	61%
10		LiTMP, –90 °C	 **2d**	25%[b]
11		LiTMP, –90 °C	 **2e**	27%
12		LiTMP, –90 °C	 **10**	18%[b]
13		LiTMP, –90 °C	 **11**	17%[b]
14		LiTMP, –90 °C	**12**	21%[b]

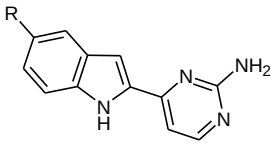
15		LiTMP, –90 °C	 **13**	20%[b]
16		BuLi, 25 °C[c]	 **14**	64%
17		LiTMP, –75 °C	 **15**	62%

[a] Coupling step performed in presence of DME (5 equiv).[14g]
[b] Since 2,4-dichloropyrimidine rapidly reacts with air damp, lower yields can be partly attributed to the presence of pyrimidinone in the starting heteroaryl chloride. [c] 2 h instead of 1 h.

Meridianins are a family of compounds isolated and characterized from the south atlantic tunicate *Aplidium Meridianum*.[28] Some of them proved to inhibit GSK-3 (Glycogen Synthase Kinase),[29] a kinase involved in the abnormal phosphorylation of tau protein and the production of β amyloid, two processes implicated in Alzheimer's disease[30] (Scheme 1).



Meridianin B (R^1 = OH, R^2 = Br, R^3 = H): 0.5 μM
Meridianin E (R^1 = OH, R^2 = H, R^3 = Br): 2.5 μM

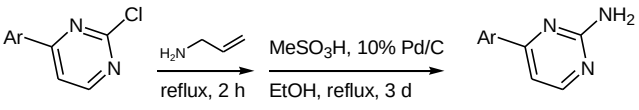


Isomeridianin C (R = Br): > 1000 μM
Isomeridianin G (R = H): 420 μM

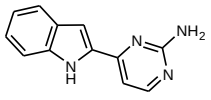
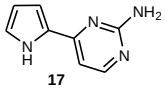
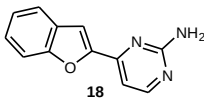
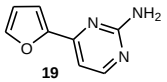
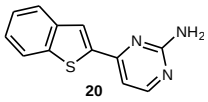
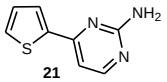
Scheme 1 Inhibition Activities (IC_{50}) at GSK-3β of Meridianins B and E, and Isomeridianins C and G

The method we developed proved suitable to prepare Isomeridianin G as well as different analogues.[31] The replacement of the indole ring by other five-membered aromatic heterocycles was first considered. To this purpose, the chloro group of 2-chloropyrimidyl compounds **2d**, **9a**, **5a**, **6**, **7a** and **1e** was substituted with allylamine to afford the derivatives **16**-**21** after subsequent cleavage of the allyl group under classical conditions[32] (Table 3).

Table 3 Synthesis of Isomeridianin G and Pyrimidine Analogues



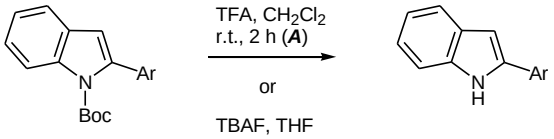
2d,**9a**,**5a**,**6**,**7a**,**1e** **16-21**

Entry	Substrate	Product	Yield (2 steps)
1	**2d**	 **16** (isomeridianin G)	48%[a]
2	**9a**	 **17**	70%[a]
3	**5a**	 **18**	55%
4	**6**	 **19**	26%
5	**7a**	 **20**	58%
6	**1e**	 **21**	29%

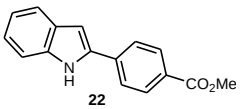
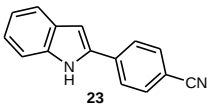
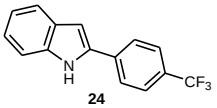
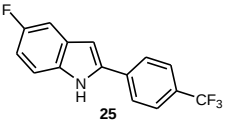
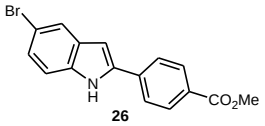
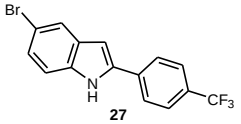
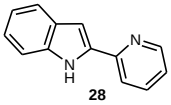
[a] Cleavage of the Boc protection occured during the first step.

The replacement of the pyrimidine group by other six-membered ring aromatics was then considered. This was achieved by cleavage of the Boc protective group of coupled compounds using either trifluoroacetic acid (TFA) in dichloromethane at r.t.[33] or tetrabutylammonium fluoride (TBAF) under reflux of THF[34] to provide the indole analogues **22**-**28** (Table 4).

Table 4 Synthesis of Indole Analogues



2a-**c**,**e**,**3**,**4a**,**b** **22-28**

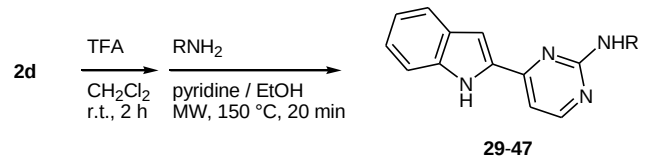
Entry	Substrate	Method	Product	Yield
1	**2a**	***A***	 **22**	52%
2	**2b**	***A***	 **23**	46%
3	**2c**	***B***	 **24**	55%
4	**3**	***A***	 **25**	46%
5	**4a**	***A***	 **26**	31%
6	**4b**	***A***	 **27**	30%
7	**2e**	***B***	 **28**	67%

Finally, analogues containing both indole and pyrimidine rings with diverse amino groups on the 2-position of the

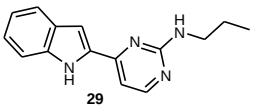
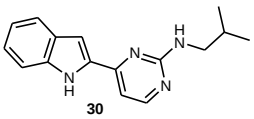
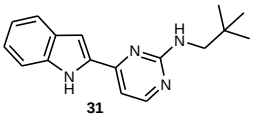
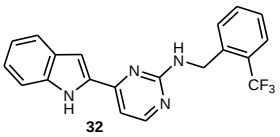
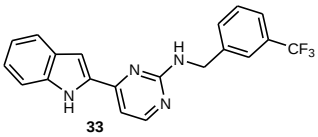
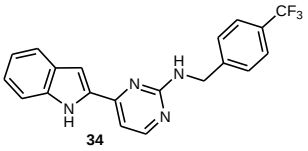
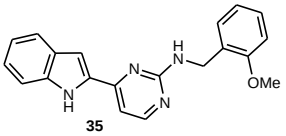
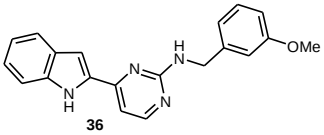
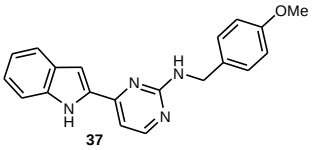
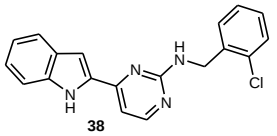
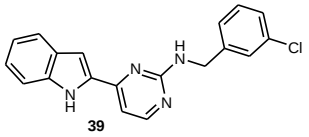
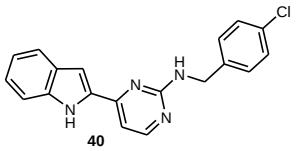
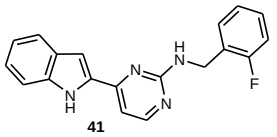
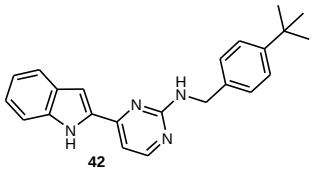
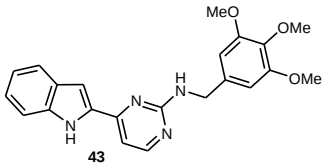
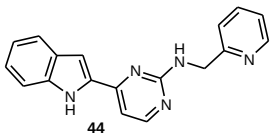
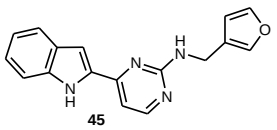
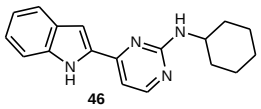
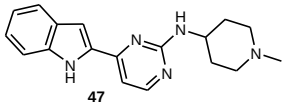
pyrimidyl ring were synthesized from the chloro compound **2d**. The substitution of the chloro group was performed using a large range of amines under microwave irradiation[35] after initial Boc cleavage using TFA.

The GSK-3β inhibition activity (IC_{50} values) of the Isomeridianin G analogues **16**-**47** was evaluated. While most of the compounds were showing a weak activity (IC_{50} > 27 μM), analogues **29**, **31**, **33**, **44** and **46** were however found to inhibit GSK-3β in the 5-25 μM range (Table 5).

Table 5 Synthesis of Both Pyrimidine and Indole Analogues of Isomeridianin G, and Inhibition Activities at GSK-3β.



29-**47**

Entry	Product	Yield (2 steps)	IC_{50} (μM)
1	 **29**	44%	20.4
2	 **30**	48%	> 27
3	 **31**	59%	11.5
4	 **32**	45%	> 27
5	 **33**	33%	24.5
6	 **34**	49%	> 27
7	 **35**	50%	> 27
8	 **36**	43%	> 27
9	 **37**	42%	> 27
10	 **38**	36%	> 27
11	 **39**	10%	> 27
12	 **40**	12%	> 27
13	 **41**	41%	> 27
14	 **42**	43%	> 27
15	 **43**	37%	> 27
16	 **44**	73%	4.9
17	 **45**	65%	> 27
18	 **46**	70%	13.8
19	 **47**	50%	> 27

In conclusion, several analogues of Isomeridianin G have been synthesized and evaluated as GSK-3β inhibitors. The key step of their synthesis is a palladium-catalyzed cross-coupling between an aromatic halide and a lithium triorganozincate which has been prepared by deprotolithiation followed by transmetalation using $ZnCl_2$·TMEDA (1/3 equiv). As compared with Isomeridianin G (IC_{50} = 420 μM), the inhibition activity at GSK-3β has been greatly improved, with an IC_{50} value of 4.9 μM for the best compound **44**. It would be interesting to make further analogues of compound **44** containing an hydroxy group at the 4-position or/and a bromo group at the 6- or 7-position, such as Meridianin templates.

Metalation reactions were performed under argon atmosphere. THF was distilled over sodium/benzophenone. LiTMP was prepared in situ in THF at 0 °C from 2,2,6,6-tetramethylpiperidine and butyllithium, and a 1.6 M butyllithium in hexanes solution was used. $ZnCl_2$·TMEDA was prepared as described previously.[36] Column chromatography separations were achieved on silica gel (40–63 μm). Mass-Directed AutoPreparative HPLC (MDAP) were performed using a Waters ZQ instrument with H_2O/acetonitrile as a gradient. Melting points were measured on a Kofler apparatus. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ARX-200 spectrometer at 200 and 50 MHz, respectively, on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively, or even on a Bruker AC-400 spectrometer at 400 and 100 MHz, respectively. ^1H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts relative to the central peak of the solvent signal.[37] Low resolution mass spectra measurements were performed using a Waters ZQ instrument in ElectroSpray Chemical Ionization (ESCI) mode. High Resolution Mass Spectra (HRMS) measurements and elemental analyses were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using a Micromass MS/MS ZABSpec TOF instrument in EI mode and a Thermo-Finnigan Flash EA 1112 CHNS analyzer, respectively. The reactions under microwave irradiation were performed in a Biotage Initiator instrument. Kinase inhibition activity at GSK-3β of Isomeridianin G and analogues was measured at GlaxoSmithKline R&D Harlow from an *in-vitro* assay, following an in-house procedure.

General Procedure for the Synthesis of *N*-Boc Protected Indoles.[19]

To a stirred solution of the required indole (35 mmol) in CH_2Cl_2 (70 mL) were successively added pyridine (3.7 mL, 45 mmol), Boc_2O (9,9 g, 45 mmol) and DMAP (0,43 g, 3,5 mmol). The mixture was stirred for 24 h at r.t. before addition of an aq sat. solution of NH_4Cl (50 mL) and extraction with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure before purification by chromatography on silica gel (the eluent is given in the product description).

***N*-Boc indole**.

Eluent: heptane/CH_2Cl_2 50/50.

Yield: 67% (5.1 g).

Colourless oil.

^1H NMR (200 MHz, $CDCl_3$): δ 1.67 (s, 9H), 6.56 (d, 1H, J = 3.5 Hz), 7.17-7.40 (m, 2H), 7.56 (m, 1H), 7.60 (d, 1H, J = 3.5 Hz), 8.19 (d, 1H, J = 8.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (3C), 83.7, 107.4, 115.3, 121.1, 122.8, 124.3, 126.0, 130.7, 135.3, 149.9.

The spectral data were found identical to those of a commercial sample.

***N*-Boc 5-nitroindole**.[38]

Eluent: hexane/CH_2Cl_2 95/5 to 50/50.

Yield: 99% (9.0 g).

White powder.

Mp 115 °C.

^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 9H), 6.71 (d, 1H, J = 4.0 Hz), 7.73 (d, 1H, J = 4.0 Hz), 8.19 (dd, 1H, J = 9.2, 2.4 Hz), 8.26 (d, 1H, J = 9.2 Hz), 8.48 (d, 1H, J = 2.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (3C), 85.4, 108.1, 115.5, 117.5, 119.7, 129.1, 130.5, 138.5, 143.9, 149.2.

ESCI MS: *m/z* 262.81, $[M+H]^+$; 206.77.

Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.26): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.53; H, 5.33; N, 10.44%.

***N*-Boc 5-cyanoindole**.

Eluent: hexane/CH_2Cl_2 95/5 to 50/50.

Yield: 97% (8.2 g).

White powder.

Mp 128 °C (lit.[39] 128-129 °C).

^1H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 9H), 6.62 (dd, 1H, J = 3.9, 0.9 Hz), 7.56 (dd, 1H, J = 8.5, 1.7 Hz), 7.70 (d, 1H, J = 3.9 Hz), 7.89 (dd, 1H, J = 1.7, 0.9 Hz), 8.25 (d, 1H, J = 8.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (3C), 85.2, 106.3, 107.2, 116.2, 120.1, 126.0, 127.6, 128.3, 130.7, 137.3, 149.3.

ESCI MS: *m/z* 242.92, $[M+H]^+$; 186.90.

Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.79; N, 11.58%.

The spectral data were found identical to those previously described.[39]

***N*-Boc 4-methoxyindole**.

Eluent: hexane/CH_2Cl_2 95/5 to 50/50.

Yield: 88% (7.5 g).

Colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 9H), 3.94 (s, 3H), 6.67 (d, 1H, J = 7.9 Hz), 6.69 (dd, 1H, J = 3.9, 0.9 Hz), 7.23 (dd, 1H, J = 8.3, 7.9 Hz), 7.50 (d, 1H, J = 3.9 Hz), 7.75 (d, 1H, J = 8.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 (3C), 55.6, 83.9, 103.2, 104.5, 108.5, 121.0, 124.6, 125.3, 136.7, 150.1, 153.1.

Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.87; N, 5.64%.

***N*-Boc 4-bromoindole**.

Eluent: hexane/CH_2Cl_2 100/0 to 50/50.

Yield: 91% (9.4 g).

Colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 9H), 6.64 (d, 1H, J = 3.9 Hz), 7.16 (dd, 1H, J = 8.3, 7.9 Hz), 7.39 (dd, 1H, J = 7.9, 0.9 Hz), 7.64 (d, 1H, J = 3.9 Hz), 8.11 (d, 1H, J = 8.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (3C), 84.5, 107.3, 114.4, 114.9, 125.3, 125.7, 126.7, 131.3, 135.8, 149.7.

Anal. Calcd for $C_{13}H_{14}BrNO_2$ (296.16): C, 52.72; H, 4.76; N, 4.73. Found: C, 52.70; H, 4.66; N, 4.72%.

***N*-Boc 5-fluoroindole**.

Eluent: heptane/CH_2Cl_2 60/40.

Yield: 70% (5.7 g).

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (s, 9H), 6.52 (d, 1H, J = 3.7 Hz), 7.03 (ddd, 1H, J = 9.2, 9.0, 2.5 Hz), 7.21 (dd, 1H, J = 9.2, 2.5 Hz), 7.63 (d, 1H, J = 3.7 Hz), 8.09 (dd, 1H, J = 9.0, 4.5 Hz).

These data were found identical to those previously described.[40]

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.4 (3C), 84.1, 106.5 (d, J = 23 Hz), 107.1 (d, J = 3.9 Hz), 112.2 (d, J = 25 Hz), 116.2 (d, J = 9.3 Hz), 127.6 (2C), 131.6 (d, J = 10 Hz), 149.7, 159.4 (d, J = 239 Hz).

***N*-Boc 5-bromoindole**.

Eluent: heptane/CH_2Cl_2 60/40.

Yield: 97% (10 g).

Brown-purple powder.

Mp 56 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (s, 9H), 6.51 (d, 1H, J = 3.5 Hz), 7.39 (dd, 1H, J = 9.1, 2.0 Hz), 7.59 (d, 1H, J = 3.5 Hz), 7.68 (d, 1H, J = 2.0 Hz), 8.02 (d, 1H, J = 9.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (3C), 84.3, 106.7, 116.2, 116.8, 123.7 (2C), 127.2, 132.4, 134.1, 149.6.

These data were found identical to those previously described.[41]

General Procedure for the Deprotonation/Cross-coupling Sequence (Compounds 1a,**c-e**, **2a-e**, **3**, **4a**,**b**, **5a**, **6**, **7a**,**b**, **8**, **9a-b**, **10-15)**.

To a stirred and cooled solution (temperature given in the product description) of the appropriate reagent (4.0 mmol) in dry THF (5 mL) under argon were added the required base (4.0 mmol) and, 1 h later, $ZnCl_2$·TMEDA[35] (0.33 g, 1.3 mmol). The mixture was slowly warmed to r.t. (1 h) before addition of the appropriate aromatic halide (4.0 mmol), $PdCl_2$ (14 mg, 80 μmol) and dppf (44 mg, 80 μmol), and heated at 55 °C for 12 h. The mixture was cooled before addition of water (0.5 mL). Extraction with EtOAc (2 x 25 mL), drying over Na_2SO_4, and removal of the solvents under reduced pressure afforded a crude compound which was purified by chromatography on silica gel (the eluent is given in the product description).

2-(4-Methoxyphenyl)thiophene (1a) was prepared from thiophene (0.32 mL) using BuLi at –75 °C and 4-bromoanisole (0.50 mL).

Eluent: heptane/CH_2Cl_2 100/0 to 95/5.

Yield: 10% (67 mg).

Beige powder.

Mp 104 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.92 (d, 2H, J = 8.8 Hz), 7.05 (dd, 1H, J = 5.0, 3.5 Hz), 7.21 (m, 2H), 7.55 (d, 2H, J = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.3, 114.2 (2C), 122.0, 123.8, 127.2 (2C), 127.4, 127.9, 144.3, 159.1.

The spectral data were found identical to those previously described.[42]

Methyl 4-(2-thienyl)benzoate (1c) was prepared from thiophene (0.32 mL) using BuLi at –75 °C and methyl 4-bromobenzoate (0.86 g).

Eluent: heptane/CH_2Cl_2 100/0 to 80/20.

Yield: 41% (0.36 g).

White powder.

Mp 134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.12 (dd, 1H, J = 4.9, 3.6 Hz), 7.36 (dd, 1H, J = 5.1, 1.1 Hz), 7.42 (dd, 1H, J = 3.6, 1.3 Hz), 7.67 (d, 2H, J = 8.8 Hz), 8.04 (d, 2H, J = 8.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 53.8, 124.4, 125.5 (2C), 126.2, 128.4, 129.1, 130.2 (2C), 138.5, 143.1, 166.7.

The spectral data were found identical to those previously described.[43]

2-(4-Cyanophenyl)thiophene (1d) was prepared from thiophene (0.32 mL) using BuLi at –75 °C and 4-bromobenzonitrile (0.73 g).

Eluent: heptane/CH_2Cl_2 100/0 to 80/20.

Yield: 79% (0.54 g).

White powder.

Mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.13 (dd, 1H, J = 4.9, 3.7 Hz), 7.40 (dd, 1H, J = 5.1, 1.2 Hz), 7.43 (dd, 1H, J = 3.7, 1.2 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.70 (d, 2H, J = 8.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 110.3, 118.7, 125.0, 125.9, 127.0, 128.4 (2C), 132.6 (2C), 138.5, 141.9.

The spectral data were found identical to those previously described.[44]

***N*-Boc 2-(4-methoxycarbonylphenyl)indole (2a)**[45] was prepared from *N*-Boc indole (0.81 mL) using LiTMP at –90 °C and methyl 4-bromobenzoate (0.86 g).

Eluent: heptane/CH_2Cl_2 70/30.

Yield: 48% (0.68 g).

White powder.

Mp 190 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.29 (s, 9H), 3.92 (s, 3H), 6.68 (s, 1H), 7.16-7.41 (m, 2H), 7.49-7.62 (m, 3H), 8.08 (m, 2H), 8.26 (d, 1H, J = 7.5 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 28.6 (3C), 53.3, 85.3, 112.5, 116.8, 122.6, 124.8, 126.4, 130.5 (2C), 130.7 (2C), 130.9 (2C), 139.5, 141.0, 141.1, 151.4, 167.8.

Anal. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.96; H, 6.14; N, 4.13%.

***N*-Boc 2-(4-cyanophenyl)indole (2b)** was prepared from *N*-Boc indole (0.81 mL) using LiTMP at –90 °C and 4-bromobenzonitrile (0.73 g).

Eluent: heptane/CH_2Cl_2 70/30.

Yield: 61% (0.78 g).

White powder.

Mp 121 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.35 (s, 9H), 6.80 (s, 1H), 7.22-7.44 (m, 2H), 7.64 (dd, 1H, J = 7.5, 1.1 Hz), 7.72 (m, 2H), 7.88 (m, 2H), 8.22 (d, 1H, J = 8.5 Hz).

These data were found identical to those previously described.[46]

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 28.7 (3C), 85.8, 112.8, 113.1, 117.0, 117.6, 122.8, 125.1, 126.8, 131.0, 131.4 (2C), 133.6 (2C), 139.6, 140.5, 141.3, 151.5.

HRMS: calcd for $C_{20}H_{18}N_2O_2$ (M^+) 318.1368, found 318.1391.

Anal. Calcd for $C_{20}H_{18}N_2O_2$ (318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.46; H, 5.80; N, 8.72%.

***N*-Boc 2-(4-trifluoromethylphenyl)indole (2c)** was prepared from *N*-Boc indole (0.81 mL) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.55 mL).

Eluent: heptane/toluene 80/20 to 40/60.

Yield: 60% (0.86 g).

White powder.

Mp 104 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.34 (s, 9H), 6.62 (s, 1H), 7.29 (dd, 1H, *J* = 7.5, 1.5 Hz), 7.37 (ddd, 1H, *J* = 8.3, 7.5, 1.5 Hz), 7.51-7.61 (m, 3H), 7.67 (d, 2H, *J* = 8.3 Hz), 8.21 (d, 1H, *J* = 8.3 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 27.6 (3C), 83.9, 111.0, 115.3, 120.7, 123.2, 124.2 (q, *J* = 272 Hz), 124.7, 124.8 (2C), 128.9 (2C), 129.0, 129.6 (q, *J* = 32 Hz), 137.5, 138.5, 138.8, 149.9.

These data were found identical to those previously described.[47]

***N*-Boc 5-fluoro-2-(4-trifluoromethylphenyl)indole (3)** was prepared from *N*-Boc 5-fluoroindole (0.59 g) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.34 mL).

Eluent: heptane/CH_2Cl_2 100/0 to 70/30.

Yield: 36% (0.34 g).

Yellow powder.

Mp 117 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.32 (s, 9H), 6.75 (s, 1H), 7.16 (ddd, 1H, *J* = 9.0, 8.3, 3.0 Hz), 7.35 (dd, 1H, *J* = 8.3, 3.0 Hz), 7.72 (d, 2H, *J* = 8.3 Hz), 7.82 (d, 2H, *J* = 8.3 Hz), 8.22 (dd, 1H, *J* = 9.0, 3.0 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 28.6 (3C), 85.9, 107.9 (d, *J* = 24 Hz), 112.2 (d, *J* = 4.4 Hz), 114.1 (d, *J* = 25 Hz), 118.3 (d, *J* = 9.9 Hz), 126.6 (2C), 128.1 (q, *J* = 214 Hz), 131.1 (q, *J* = 31 Hz), 131.3 (2C), 131.9 (d, *J* = 11 Hz), 135.9, 140.5, 142.4, 151.3, 161.2 (d, *J* = 238 Hz).

HRMS: calcd for $C_{20}H_{17}F_4NO_2$ (M^+) 379.1195, found 379.1183.

***N*-Boc 5-bromo-2-(4-methoxycarbonylphenyl)indole (4a)** was prepared from *N*-Boc 5-bromoindole (1.2 g) using LiTMP at –90 °C and methyl 4-bromobenzoate (0.86 g).

Eluent: heptane/CH_2Cl_2 50/50 to 40/60.

Yield: 66% (1.1 g).

Beige powder.

Mp 154 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.31 (s, 9H), 3.92 (s, 3H), 6.74 (s, 1H), 7.49 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.65 (d, 2H, *J* = 8.6 Hz), 7.81 (d, 1H, *J* = 2.0 Hz), 8.10 (d, 2H, *J* = 8.6 Hz), 8.15 (d, 1H, *J* = 8.5 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 28.6 (3C), 53.4, 86.1, 111.5, 117.6, 118.7, 125.1, 129.1, 130.7 (2C), 130.9, 131.4 (2C), 132.8, 138.3, 140.7, 142.5, 151.2, 167.9.

HRMS: calcd for $C_{21}H_{20}{}^{79}BrNO_4$ (M^+) 429.0576, found 429.0543.

Anal. Calcd for $C_{21}H_{20}BrNO_4$ (430.29): C, 58.62; H, 4.69; N, 3.26. Found: C, 58.59; H, 4.89; N, 3.29%.

***N*-Boc 5-bromo-2-(4-trifluoromethylphenyl)indole (4b)** was prepared from *N*-Boc 5-bromoindole (1.2 g) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.54 mL).

Eluent: heptane/CH_2Cl_2 100/0 to 60/40.

Yield: 31% (0.54 g).

White powder.

Mp 104 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.31 (s, 9H), 6.70 (s, 1H), 7.46 (dd, 1H, *J* = 9.1, 2.0 Hz), 7.59-7.85 (m, 5H), 8.15 (d, 1H, *J* = 9.1 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 28.5 (3C), 86.0, 111.6, 117.7, 118.7, 125.1, 125.8 (q, *J* = 271 Hz), 126.6 (q, 2C, *J* = 3.9 Hz), 129.1, 130.6 (q, *J* = 32 Hz), 131.3 (2C), 132.7, 138.1, 140.1 (q, *J* = 1.6 Hz), 141.9, 151.1.

HRMS: calcd for $C_{20}H_{17}{}^{79}BrF_3NO_2$ (M^+) 439.0394, found 439.0401.

4-(2-Benzo[*b*]furyl)-2-chloropyrimidine (5a) was prepared from benzo[*b*]furan (0.44 mL) using BuLi at –15 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: CH_2Cl_2/MeOH 100/0 to 80/20.

Yield: 56% (0.52 g).

Pale yellow powder.

Mp 186 °C.

^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 7.37 (t, 1H, *J* = 7.8 Hz), 7.51 (t, 1H, *J* = 7.8 Hz), 7.69 (d, 1H, *J* = 7.8 Hz), 7.82 (d, 1H, *J* = 7.8 Hz), 7.90 (s, 1H), 7.97 (d, 1H, *J* = 5.2 Hz), 8.86 (d, 1H, *J* = 5.2 Hz).

The ^{1}H NMR spectrum was found identical to that previously described.[23]

^{13}C NMR (50 MHz, $(CD_3)_2CO$): δ 110.9, 112.4, 114.5, 123.5, 124.7, 127.8, 128.5, 152.2, 156.5, 158.6, 161.8, 162.1.

HRMS: calcd for $C_{12}H_7{}^{35}ClN_2O$ (M^+) 230.0247, found 230.0238.

Anal. Calcd for $C_{12}H_7ClN_2O$ (230.65): C, 62.49; H, 3.06; N, 12.15. Found: C, 62.75; H, 3.13; N, 12.35%.

2-Chloro-4-(2-furyl)pyrimidine (6) was prepared from furan (0.29 mL) using BuLi at –15 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: heptane/EtOAc 100/0 to 80/20.

Yield: 61% (0.45 g).

White powder.

Mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.60 (dd, 1H, *J* = 3.5, 1.5 Hz), 7.38 (dd, 1H, *J* = 3.5, 1.0 Hz), 7.51 (d, 1H, *J* = 5.2 Hz), 7.63 (m, 1H), 8.57 (d, 1H, *J* = 5.2 Hz).

The ^{1}H NMR spectrum was found identical to that previously described.[23]

^{13}C NMR (50 MHz, $CDCl_3$): δ 113.1, 113.1, 114.5, 146.2, 150.4, 158.1, 159.9, 161.7.

4-(2-Benzo[*b*]thienyl)-2-chloropyrimidine (7a) was prepared from benzo[*b*]thiophene (0.54 g) using BuLi at –75 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: heptane/EtOAc 100/0 to 70/30.

Yield: 29% (0.29 g).

Pale yellow powder.

Mp 198 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.46 (m, 2H), 7.59 (d, 1H, *J* = 5.5 Hz), 7.82-7.92 (m, 2H), 8.12 (s, 1H), 8.60 (d, 1H, *J* = 5.5 Hz).

The ^{1}H NMR spectrum was found identical to that previously described.[23]

^{13}C NMR (50 MHz, $CDCl_3$): δ 114.5, 122.9, 125.2, 125.3, 126.3, 126.9, 139.8, 140.1, 141.8, 159.7, 161.9, 162.3.

2-(2-Benzo[*b*]thienyl)pyridine (7b) was prepared from benzo[*b*]thiophene (0.54 g) using BuLi at –75 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/CH_2Cl_2 50/50 to 30/70.

Yield: 81% (0.69 g).

White powder.

Mp 126 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21 (m, 1H), 7.36 (m, 2H), 7.73 (dt, 1H, *J* = 8.0, 1.6 Hz), 7.81 (m, 4H), 8.64 (d, 1H, *J* = 5.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 119.6, 121.1, 122,6 (2C), 124.1, 124.5, 125.0, 136.6, 140.5, 140.6, 144.8, 149.7, 152.5.

The spectral data were found identical to those of a commercial sample.

HRMS: calcd for $C_{13}H_9NS$ (M^+) 211.0456, found 211.0461.

2-Chloro-4-(2-thienyl)pyrimidine (1e) was prepared from thiophene (0.32 mL) using BuLi at –75 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: heptane/EtOAc 100/0 to 80/20.

Yield: 56% (0.44 g).

White powder.

Mp 124 °C.

The physical data were found identical to those previously described.[48]

^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 7.17 (dd, 1H, *J* = 7.5, 5.7 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.59 (dd, 1H, *J* = 7.5, 1.5 Hz), 7.82 (dd, 1H, *J* = 5.7, 1.5 Hz), 8.53 (d, 1H, *J* = 8.1 Hz).

^{13}C NMR (50 MHz, $(CD_3)_2CO$): δ 113.7, 128.8, 129.2, 131.8, 140.5, 159.5, 161.7, 162.0.

2-(5-Chlorothienyl)pyridine (8) was prepared from 2-chlorothiophene (0.37 mL) using BuLi at –75 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/EtOAc 100/0 to 80/20.

Yield: 85% (0.67 g).

Pale yellow powder.

Mp 67 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (d, 1H, *J* = 3.8 Hz), 7.15 (ddd, 1H, *J* = 7.1, 4.9, 1.5 Hz), 7.33 (d, 1H, *J* = 3.8 Hz), 7.56 (dt, 1H, *J* = 8.1, 1.0 Hz), 7.66 (ddd, 1H, *J* = 9.1, 7.6, 2.0 Hz), 8.53 (dq, 1H, *J* = 4.9, 1.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 117.2, 121.5, 122.9 (CH), 126.7, 131.4, 135.9, 143.0, 148.7, 150.8.

The spectral data were found identical to those previously described.[49]

***N*-Boc 2-(2-chloro-4-pyrimidyl)indole (9a)** was prepared from *N*-Boc indole (0.82 mL) using LiTMP at –75 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: hexane/CH_2Cl_2 70/30 to 30/70.

Yield: 25% (0.33 g).

Beige powder.

Mp 114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 7.02 (d, 1H, *J* = 0.9 Hz), 7.28 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.43 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.45 (d, 1H, *J* = 5.3 Hz), 7.62 (ddd, 1H, *J* = 7.9, 1.3, 0.9 Hz), 8.17 (dd, 1H, *J* = 8.3, 0.9 Hz), 8.64 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (3C), 84.9, 115.1, 115.4, 117.9, 122.0, 123.7, 126.9, 128.4, 135.6, 138.9, 149.7, 159.4, 161.1, 163.0.

Anal. Calcd for $C_{17}H_{16}ClN_3O_2$ (329.78): C, 61.91; H, 4.89; N, 12.74. Found: C, 61.90; H, 4.86; N, 12.69%.

***N*-Boc 2-(2-pyridyl)pyrrole (9b)** was prepared from *N*-Boc pyrrole (0.67 mL) using LiTMP at –75 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/CH_2Cl_2 70/30 to 0/100.

Yield: 61% (0.60 g).

Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 9H), 6.18 (t, 1H, *J* = 3.2 Hz), 6.36 (dd, 1H, *J* = 3.5, 1.5 Hz), 7.07-7.19 (m, 1H), 7.29-7.39 (m, 2H), 7.61 (ddd, 1H, *J* = 9.6, 7.5, 1.5 Hz), 8.56 (d, 1H, *J* = 4.5 Hz).

The spectral data were found identical to those previously described.[50]

***N*-Boc 2-(2-chloro-4-pyrimidyl)pyrrole (2d)** was prepared from *N*-Boc pyrrole (0.67 mL) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: heptane/CH_2Cl_2 50/50 to 0/100.

Yield: 25% (0.26 g).

Beige powder.

Mp 102 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 6.25 (t, 1H, *J* = 3.5 Hz), 6.69 (dd, 1H, *J* = 3.5, 2.0 Hz), 7.31 (d, 1H, *J* = 5.5 Hz), 7.41 (dd, 1H, *J* = 3.5, 2.0 Hz), 8.51 (d, 1H, *J* = 5.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.7 (3C), 85.1, 111.4, 117.6, 120.0, 127.1, 130.5, 148.8, 158.9, 160.7, 161.9.

HRMS: calcd for $C_{13}H_{14}{}^{35}ClN_3O_2$ (M^+) 279.0774, found 279.0787.

***N*-Boc 2-(2-pyridyl)indole (2e)**[51] was prepared from *N*-Boc indole (0.81 mL) using LiTMP at –90 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/CH_2Cl_2 60/40 to 0/100.

Yield: 27% (0.32 g).

Brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.77 (s, 1H), 7.22-7.29 (m, 2H), 7.36 (ddd, 1H, *J* = 8.3, 6.8, 1.5 Hz), 7.51 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.74 (ddd, 1H, *J* = 8.3, 7.5, 1.5 Hz), 8.19 (d, 1H, *J* = 7.5 Hz), 8.67 (d, 1H, *J* = 6.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 (3C), 83.4, 111.0, 115.0, 120.9, 122.2, 122.9, 123.3, 124.9, 128.8, 136.0, 137.7, 139.3, 148.9, 150.0, 153.3.

HRMS: calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368, found 294.1352.

Anal. Calcd for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.14; H, 6.05; N, 9.30%.

***N*-Boc 2-(2-chloro-4-pyrimidyl)-4-methoxyindole (10)** was prepared from *N*-Boc 4-methoxyindole (1.0 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: hexane/CH_2Cl_2 40/60 to 0/100.

Yield: 18% (0.26 g).

Yellow powder.

Mp 148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.95 (s, 3H), 6.69 (d, 1H, *J* = 7.9 Hz), 7.16 (s, 1H), 7.34 (dd, 1H, *J* = 8.3, 7.9 Hz), 7.44 (d, 1H, *J* = 5.3 Hz), 7.74 (d, 1H, *J* = 8.3 Hz), 8.61 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (3C), 55.7, 84.8, 103.5, 108.1, 112.5, 117.6, 119.2, 128.0, 134.1, 140.3, 149.8, 153.9, 159.3, 161.1, 162.9.

ESCI MS: *m/z* 303.79, 305.74 [M+H-^{t}Bu]$^+$; 259.80, 261.73 [M+H-Boc]$^+$.

***N*-Boc 4-bromo-2-(2-chloro-4-pyrimidyl)indole (11)** was prepared from *N*-Boc 4-bromoindole (1.2 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: hexane/CH_2Cl_2 40/60 to 0/100.

Yield: 17% (0.28 g).

Beige powder.

Mp 125-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 7.06 (d, 1H, *J* = 0.9 Hz), 7.29 (dd, 1H, *J* = 8.3, 7.9 Hz), 7.45 (dd, 1H, *J* = 7.9, 0.9 Hz), 7.50 (d, 1H, *J* = 4.8 Hz), 8.12 (ddd, 1H, *J* = 8.3, 1.2, 0.9 Hz), 8.68 (d, 1H, *J* = 4.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8 (3C), 85.4, 114.3, 114.5, 115.7, 118.0, 126.5, 127.6, 129.2, 136.0, 139.0, 149.3, 159.7, 161.2, 162.6.

ESCI MS: *m/z* 353.76, 355.79 [M+H-^{t}Bu]$^+$; 307.85, 309.82 [M+H-Boc]$^+$.

***N*-Boc 2-(2-chloro-4-pyrimidyl)-5-cyanoindole (12)** was prepared from *N*-Boc 5-cyanoindole (0.97 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: hexane/CH_2Cl_2 50/50 to 0/100.

Yield: 21% (0.29 g).

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 6.98 (s, 1H), 7.50 (d, 1H, *J* = 4.8 Hz), 7.60 (dd, 1H, *J* = 8.7, 1.7 Hz), 7.91 (dd, 1H, *J* = 1.7, 0.9 Hz), 8.21 (d, 1H, *J* = 8.7 Hz), 8.69 (d, 1H, *J* = 4.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6 (3C), 85.9, 106.9, 113.3, 116.2, 118.0, 119.4, 126.7, 128.1, 129.2, 137.4, 140.0, 148.6, 159.9, 161.0, 162.0.

ESCI MS: *m/z* 298.88, 300.88 [M+H-^{t}Bu]$^+$; 254.87, 256.86 [M+H-Boc]$^+$.

***N*-Boc 2-(2-chloro-4-pyrimidyl)-5-nitroindole (13)** was prepared from *N*-Boc 5-nitroindole (1.05 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g).

Eluent: hexane/CH_2Cl_2 50/50 to 0/100.

Yield: 20% (0.30 g).

Yellow powder.

Mp > 260 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 7.09 (s, 1H), 7.51 (d, 1H, *J* = 5.3 Hz), 8.29-8.31 (m, 2H), 8.56 (dd, 1H, *J* = 1.7, 0.9 Hz), 8.73 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8 (3C), 86.4, 114.2, 115.8, 118.1, 118.3, 121.7, 128.0, 138.5, 141.1, 144.4, 148.8, 160.1, 161.3, 162.1.

ESCI MS: *m/z* 318.73, 320.73 [M+H-^{t}Bu]$^+$; 274.78, 276.71 [M+H-Boc]$^+$.

2-(2-Methoxyphenyl)pyridine (14) was prepared from anisole (0.44 mL) using BuLi at 25 °C and 2-chloropyridine (0.38 mL).

Eluent: CH_2Cl_2.

Yield: 64% (0.43 g).

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 7.02 (d, 1H, *J* = 8.3 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 7.2 (m, 1H), 7.37 (dt, 1H, *J* = 7.8, 1.7 Hz), 7.7 (m, 3H), 8.71 (dd, 1H, *J* = 4.3, 1.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0, 111.7, 121.4, 122.0, 125.5, 129.5, 130.3, 131.5, 136.0, 149.8, 156.4, 157.2.

The spectral data were found identical to those previously described.[52]

2-Fluoro-3-(2-pyridyl)pyridine (15) was prepared from 2-fluoropyridine (0.34 mL) using LiTMP at –75 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/CH_2Cl_2 60/40 to 0/100.

Yield: 62% (0.43 g).

Beige powder.

Mp < 50 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25-7.37 (m, 2H), 7.72-7.91 (m, 2H), 8.25 (d, 1H, *J* = 3.2 Hz), 8.47-8.58 (m, 1H), 8.72 (d, 1H, *J* = 4.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 122.1 (d, *J* = 4.3 Hz), 122.6, 123.2, 124.3 (d, *J* = 10 Hz), 136.8, 141.6 (d, *J* = 3.8 Hz), 147.7 (d, *J* = 15 Hz), 150.0, 151.4 (d, *J* = 6.8 Hz), 160.9 (d, *J* = 241 Hz).

HRMS: calcd for $C_{10}H_7FN_2$ (M^+) 174.0593, found 174.0595.

General Procedure for the Deprotonation/Cross-coupling Sequence (Compounds 1b and 5b).

To a stirred and cooled solution (temperature given in the product description) of the appropriate reagent (4.0 mmol) in dry THF (5 mL) under argon were added the required base (4.0 mmol) and, 1 h later, $ZnCl_2$·TMEDA[34] (0.33 g, 1.3 mmol). The mixture was slowly warmed to r.t. (1 h) before addition of the appropriate aromatic halide (4.0 mmol), $PdCl_2$ (14 mg, 80 μmol), dppf (44 mg, 80 μmol) and 1,2-dimethoxyethane (2.1 mL, 20 mmol), and heated at 55 °C for 12 h. The mixture was cooled before addition of water (0.5 mL). Extraction with EtOAc (2 x 25 mL), drying over Na_2SO_4, and removal of the solvents under reduced pressure afforded a crude compound which was purified by chromatography on silica gel (the eluent is given in the product description).

2-(4-Nitrophenyl)thiophene (1b) was prepared from thiophene (0.32 mL) using BuLi at –75 °C and 1-bromo-4-nitrobenzene (0.81 g).

Eluent: heptane/EtOAc 100/0 to 90/10.

Yield: 76% (0.62 g).

Yellow powder.

Mp 135 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (t, 1H, J = 4.4 Hz), 7.44 (d, 1H, J = 5.2 Hz), 7.48 (d, 1H, J = 4.0 Hz), 7.74 (d, 2H, J = 9.5 Hz), 8.23 (d, 2H, J = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 124.4, 125.7 (2C), 126.0, 127.7, 128.7 (2C), 140.6, 141.6, 146.6.

The spectral data were found identical to those previously described.[53]

2-(2-Benzo[*b*]furyl)pyridine (5b) was prepared from benzo[*b*]furan (0.44 mL) using butyllithium at –15 °C and 2-chloropyridine (0.38 mL).

Eluent: heptane/CH_2Cl_2 60/40.

Yield: 76% (0.60 g).

White powder.

Mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20-7.39 (m, 3H), 7.43 (d, 1H, J = 1.0 Hz), 7.57 (dq, 1H, J = 8.1, 1.0 Hz), 7.62-7.68 (m, 1H), 7.78 (ddd, 1H, J = 9.3, 8.1, 1.5 Hz), 7.91 (dt, 1H, J = 9.3, 1.0 Hz), 8.69 (m, 1H).

The spectral data were found identical to those previously described.[54]

General Procedure for the Substitution of the Chloro Group of Compounds 2d, 9a, 5a, 6, 7a and 1e with Allylamine and Subsequent Allyl Cleavage (Compounds 16-21).

A stirred solution of the aromatic chloride (1.0 mmol) in allylamine (5 mL) was heated under reflux for 2 h. After concentration under reduced pressure, water (10 mL) and aq 1M NaOH (1 mL) were added before extraction with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. After checking the purity by NMR, the crude allylated compound was directly dissolved in EtOH (5 mL), and $MeSO_3H$ (85 μL, 1.3 mmol) and palladium on charcoal (10%, 0.10 g) were added at r.t. The mixture was then heated under reflux for 3 days, filtrated over celite®, and the solvents were removed under reduced pressure. An aq sat. $NaHCO_3$ solution (10 mL) was added to the residue before extraction with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure before purification by chromatography on silica gel (eluent given in the product description).

4-(2-Indolyl)-2-pyrimidinamine (16, Isomeridianin G). Precursor *N*-allyl-4-(2-indolyl)-2-pyrimidinamine was prepared from *N*-Boc 2-(2-chloro-4-pyrimidyl)indole (**2d**, 0.33 g), and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.14-4.22 (m, 2H), 5.19 (dq, 1H, J = 11, 1.5 Hz), 5.26 (s, 1H), 5.31 (dq, 1H, J = 17, 1.5 Hz), 5.96-6.11 (m, 1H), 7.00 (d, 1H, J = 5.3 Hz), 7.09-7.16 (m, 2H), 7.27 (ddd, 1H, J = 8.3, 7.0, 1.5 Hz), 7.44 (d, 1H, J = 8.3 Hz), 7.66 (d, 1H, J = 7.5 Hz), 8.29 (d, 1H, J = 5.3 Hz), 9.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 44.0, 103.6, 106.1, 111.5, 115.8, 120.4, 121.6 (2C), 128.7, 135.0, 135.1, 136.5, 157.4, 158.1, 162.1.

4-(2-Indolyl)-2-pyrimidinamine (**16, Isomeridianin G**):

Eluent: EtOAc/CH_2Cl_2 70/30.

Yield: 48% (2 steps, 0.10 g).

Yellow powder.

Mp 225 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (s, 2H), 7.07 (d, 1H, J = 5.3 Hz), 7.09-7.16 (m, 2H), 7.27 (td, 1H, J = 8.3, 1.5 Hz), 7.43 (d, 1H, J = 8.3 Hz), 7.66 (d, 1H, J = 8.3 Hz), 8.28 (d, 1H, J = 5.3 Hz), 9.40 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 104.2, 106.9, 111.6, 120.5, 121.7, 124.5, 128.6, 134.2, 136.7, 157.5, 158.0, 162.9.

HRMS: calcd for $C_{12}H_{10}N_4$ (M^+) 210.0905, found 210.0884.

The physical and spectral data were found identical to those previously described.[31]

4-(2-Pyrryl)-2-pyrimidinamine (17).[55] Precursor *N*-allyl-4-(2-pyrryl)-2-pyrimidinamine was prepared from *N*-Boc 2-(2-chloro-4-pyrimidyl)pyrrole (**9a**, 0.28 g), and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.06-4.16 (m, 2H), 5.15 (dq, 1H, J = 10, 1.5 Hz), 5.27 (dq, 1H, J = 17, 1.5 Hz), 5.30 (s, 1H), 5.87-6.10 (m, 1H), 6.30 (m, 1H), 6.76 (d, 1H, J = 5.1 Hz), 6.81 (ddd, 1H, J = 3.5, 2.5, 1.2 Hz), 6.96 (ddd, 1H, J = 3.5, 2.5, 1.2 Hz), 8.18 (d, 1H, J = 5.1 Hz), 9.55 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.9, 104.6, 110.3, 110.8, 115.6, 121.1, 129.7, 135.2, 157.0, 157.6, 161.8.

4-(2-Pyrryl)-2-pyrimidinamine (**17**):

Eluent: EtOAc/CH_2Cl_2 50/50.

Yield: 70% (2 steps, 0.11 g).

Beige powder.

Mp 183 °C.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 5.80 (s, 2H), 6.18-6.24 (m, 1H), 6.88 (d, 1H, J = 5.1 Hz), 6.84-6.89 (m, 1H), 6.97-7.01 (m, 1H), 8.13 (d, 1H, J = 5.1 Hz), 10.6 (s, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 106.6, 112.3, 112.7, 124.1, 132.5, 159.8, 160.9, 165.8.

HRMS: calcd for $C_8H_8N_4$ (M^+) 160.0749, found 160.0743.

4-(2-Benzo[*b*]furyl)-2-pyrimidinamine (18). Precursor *N*-allyl-4-(2-benzo[*b*]furyl)-2-pyrimidinamine was prepared from 4-(2-benzo[*b*]furyl)-2-chloropyrimidine (**5a**, 0.23 g), and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.11-4.20 (m, 2H), 5.17 (dq, 1H, *J* = 11, 1.5 Hz), 5.30 (dq, 1H, *J* = 17, 1.5 Hz), 5.35 (s, 1H), 5.90-6.12 (m, 1H), 7.10 (d, 1H, *J* = 5.1 Hz), 7.26 (ddd, 1H, *J* = 8.6, 7.6, 1.0 Hz), 7.37 (ddd, 1H, *J* = 8.6, 7.0, 1.5 Hz), 7.52 (s, 1H), 7.56 (d, 1H, *J* = 7.0 Hz), 7.66 (dd, 1H, *J* = 7.6, 1.5 Hz), 8.40 (d, 1H, *J* = 5.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.8, 105.9, 107.4, 111.7, 115.7, 121.9, 123.3, 125.9, 128.2, 134.9, 153.7, 155.5, 156.3, 158.9, 162.2.

4-(2-Benzo[*b*]furyl)-2-pyrimidinamine (**18**):

Eluent: EtOAc.

Yield: 55% (2 steps, 0.12 g).

Pale yellow powder.

Mp 205 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (s, 2H), 7.17 (d, 1H, *J* = 5.3 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.39 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz), 7.53 (s, 1H), 7.58 (d, 1H, *J* = 8.5 Hz), 7.66 (d, 1H, *J* = 7.6 Hz), 8.39 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 106.9, 108.0, 111.8, 122.1, 123.5, 126.3, 128.2, 152.7, 155.1, 156.3, 158.9, 162.5.

HRMS: calcd for $C_{12}H_9N_3O$ (M^+) 211.0746, found 211.0745.

4-(2-Furyl)-2-pyrimidinamine (19).[55] Precursor *N*-allyl-4-(2-furyl)-2-pyrimidinamine was prepared from 4-(2-furyl)-2-chloropyrimidine (**6**, 0.18 g) , and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.07-4.17 (m, 2H), 5.15 (dq, 1H, *J* = 11, 1.5 Hz), 5.28 (dq, 1H, *J* = 17, 1.5 Hz), 5.30 (s, 1H), 5.88-6.10 (m, 1H), 6.54 (dd, 1H, *J* = 3.6, 1.5 Hz), 6.90 (d, 1H, *J* = 5.1 Hz), 7.16 (d, 1H, *J* = 3.6 Hz), 7.57 (m, 1H), 8.31 (d, 1H, *J* = 5.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.8, 104.9, 111.5, 112.1, 115.7, 135.0, 144.5, 152.2, 156.1, 158.5, 162.2.

4-(2-Furyl)-2-pyrimidinamine (**19**):

Eluent: EtOAc.

Yield: 26% (2 steps, 42 mg).

Dark yellow powder (degradation before melting).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (s, 2H), 6.54 (dd, 1H, *J* = 3.8, 2.2 Hz), 6.96 (d, 1H, *J* = 5.1 Hz), 7.14 (d, 1H, *J* = 3.8 Hz), 7.57 (s, 1H), 8.30 (d, 1H, *J* = 5.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 104.7, 110.9, 111.3, 143.5, 152.5, 156.2, 158.4, 162.6.

HRMS: calcd for $C_8H_7N_3O$ (M^+) 161.0589, found 161.0577.

4-(2-Benzo[*b*]thienyl)-2-pyrimidinamine (20). Precursor *N*-allyl-4-(2-benzo[*b*]thienyl)-2-pyrimidinamine was prepared from 4-(2-benzo[*b*]thienyl)-2-chloropyrimidine (**7a**, 0.22 g), and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.04-4.14 (m, 2H), 5.11 (dq, 1H, *J* = 11, 1.5 Hz), 5.26 (dq, 1H, *J* = 17, 1.5 Hz), 5.25 (s, 1H), 5.84-6.06 (m, 1H), 6.95 (d, 1H, *J* = 5.1 Hz), 7.27-7.35 (m, 2H), 7.72-7.84 (m, 2H), 7.88 (s, 1H), 8.25 (d, 1H, *J* = 5.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.9, 105.7, 115.9, 122.6, 123.7, 124.5, 124.6, 125.7 (2C), 134.9, 139.9, 140.9, 158.3, 159.8, 162.2.

4-(2-Benzo[*b*]thienyl)-2-pyrimidinamine (**20**):

Eluent: EtOAc.

Yield: 58% (2 steps, 0.13 g).

White powder.

Mp 230 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (s, 2H), 7.08 (d, 1H, *J* = 5.3 Hz), 7.34-7.43 (m, 2H), 7.78-7.91 (m, 2H), 7.96 (s, 1H), 8.33 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 105.2, 123.5, 124.4, 124.5, 125.6 (2C), 139.8, 140.8, 143.4, 158.2, 159.9, 162.3.

HRMS: calcd for $C_{12}H_9N_3S$ (M^+) 227.0517, found 227.0531.

4-(2-Thienyl)-2-pyrimidinamine (21). Precursor *N*-allyl-4-(2-thienyl)-2-pyrimidinamine was prepared from 4-(2-thienyl)-2-chloropyrimidine (**1e**, 0.20 g), and identified by NMR:

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.00-4.11 (m, 2H), 5.08 (dq, 1H, *J* = 10, 1.5 Hz), 5.22 (dq, 1H, *J* = 17, 1.5 Hz), 5.23 (s, 1H), 5.82-6.03 (m, 1H), 6.86 (d, 1H, *J* = 5.1 Hz), 7.11 (dd, 1H, *J* = 5.0, 3.5 Hz), 7.44 (dd, 1H, *J* = 5.0, 1.0 Hz), 7.66 (dd, 1H, *J* = 3.5, 1.0 Hz), 8.27 (d, 1H, *J* = 5.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.9, 104.6, 115.8, 126.9, 127.9, 129.5, 134.7, 140.5, 158.6, 159.4, 162.6.

4-(2-Thienyl)-2-pyrimidinamine (**21**):

Eluent: EtOAc/CH_2Cl_2 50/50.

Yield: 29% (2 steps, 51 mg).

Pale yellow powder.

Mp 181 °C (lit.[56] 174 °C).

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 6.06 (s, 2H), 7.05 (d, 1H, *J* = 5.3 Hz), 7.16 (dd, 1H, *J* = 5.3, 3.8 Hz), 7.63 (dd, 1H, *J* = 5.3, 1.5 Hz), 7.83 (dd, 1H, *J* = 3.8, 1.5 Hz), 8.25 (d, 1H, *J* = 5.3 Hz).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 105.6, 127.9, 128.9, 130.2, 144.2, 159.6, 160.4, 164.8.

HRMS: calcd for $C_8H_7N_3S$ (M^+) 177.0361, found 177.0373.

General Procedure for the Deprotection of *N*-Boc Indoles using TFA (Compounds 22, 23, 25-27).

To a stirred solution of the appropriate *N*-Boc indole (2.0 mmol) in CH_2Cl_2 (10 mL) at r.t. was added TFA (30 mmol). After 2 h at r.t., a sat. aq $NaHCO_3$ solution (10 mL) was added. Extraction with EtOAc (3 x 10 mL), washing with brine (10 mL), drying over Na_2SO_4, and removal of the solvents under reduced pressure afforded a crude product which was purified by chromatography on silica gel (eluent given in the product description).

2-(4-Methoxycarbonylphenyl)indole (22) was prepared from *N*-Boc 2-(4-methoxycarbonylphenyl)indole (**2a**, 0.71 g).

Eluent: CH_2Cl_2.

Yield: 52% (0.27 g).

Yellow powder.

Mp 200 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.95 (dd, 1H, *J* = 2.5, 1.0 Hz), 7.14 (ddd, 1H, *J* = 8.6, 7.5, 1.5 Hz), 7.24 (ddd, 1H, *J* = 8.6, 8.0, 1.5 Hz), 7.42 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.65 (d, 1H, *J* = 7.5 Hz), 7.72 (dt, 2H, *J* = 8.6, 2.0 Hz), 8.10 (dt, 2H, *J* = 8.6, 2.0 Hz), 8.47 (s, 1H).

These spectral data were found identical to those previously described.[57]

^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 101.8, 111.1, 120.6, 121.0, 123.1, 124.6 (2C), 128.8, 129.0, 130.3 (2C), 136.4, 137.2, 141.3, 166.7.

HRMS: calcd for $C_{16}H_{13}NO_2$ (M^+) 251.0946, found 251.0968.

Anal. Calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.27; H, 5.23; N, 5.54%.

2-(4-Cyanophenyl)indole (23) was prepared from *N*-Boc 2-(4-cyanophenyl)indole (**2b**, 0.64 g).

Eluent: CH_2Cl_2.

Yield: 46% (0.20 g).

Yellow powder.

Mp 192 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94 (d, 1H, *J* = 2.2 Hz), 7.10-7.28 (m, 2H), 7.42 (dd, 1H, *J* = 8.1, 7.5 Hz), 7.65 (d, 1H, *J* = 7.5 Hz), 7.68-7.74 (m, 2H), 7.85-7.88 (m, 2H), 8.37 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 101.1, 111.5, 112.7, 117.8, 120.7, 121.6, 123.2, 128.7, 131.5 (2C), 133.3 (2C), 136.1, 136.9, 141.3.

HRMS: calcd for $C_{15}H_{10}N_2$ (M^+) 218.0844, found 218.0858.

These data were found identical to those previously described.[58]

5-Fluoro-2-(4-trifluoromethylphenyl)indole (25) was prepared from *N*-Boc 5-fluoro-2-(4-trifluoromethylphenyl)indole (**3**, 0.77 g).

Eluent: heptane/CH_2Cl_2 50/50.

Yield: 46% (0.26 g).

Yellow powder.

Mp 162 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88 (d, 1H, *J* = 1.5 Hz), 6.98 (ddd, 1H, *J* = 11.6, 9.1, 2.5 Hz), 7.24-7.38 (m, 2H), 7.65-7.80 (m, 4H), 8.36 (s, 1H).

HRMS: calcd for $C_{15}H_9F_4N$ (M^+) 279.0671, found 279.0652.

These data were found identical to those previously described.[59]

5-Bromo-2-(4-methoxycarbonylphenyl)indole (26) was prepared from *N*-Boc 5-bromo-2-(4-methoxycarbonylphenyl)indole (**4a**, 0.88 g).

Eluent: heptane/CH_2Cl_2 50/50.

Yield: 31% (0.20 g).

Yellow powder.

Mp 204 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.88 (d, 1H, *J* = 2.0 Hz), 7.25-7.33 (m, 2H), 7.66-7.79 (m, 3H), 8.12 (d, 2H, *J* = 8.6 Hz), 8.46 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 101.2, 112.5, 113.7, 123.4, 124.8 (2C), 125.9, 129.3, 130.4 (2C), 130.8, 135.8, 135.9, 137.9, 167.3.

HRMS: calcd for $C_{16}H_{12}{}^{79}BrNO_2$ (M^+) 329.0051, found 329.0320.

5-Bromo-2-(4-trifluoromethylphenyl)indole (27) was prepared from *N*-Boc 5-bromo-2-(4-trifluoromethylphenyl)indole (**4b**, 0.89 g).

Eluent: heptane/CH_2Cl_2 60/40.

Yield: 30% (0.20 g).

Yellow powder.

Mp 190 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.78 (d, 1H, *J* = 2.0 Hz), 7.23 (d, 2H, *J* = 2.0 Hz), 7.58-7.73 (m, 5H), 8.34 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 101.3, 111.8, 114.7, 123.5, 124.5 (q, *J* = 253 Hz), 125.6 (q, 2C, *J* = 3.6 Hz), 125.9, 127.7 (2C), 129.3, 129.8 (q, *J* = 32 Hz), 135.7, 136.0, 140.8.

HRMS: calcd for $C_{15}H_9{}^{79}BrF_3N$ (M^+) 338.9870, found 338.9893.

General Procedure for the Deprotection of *N*-Boc Indoles using TBAF (Compounds 24, 28).

To a stirred solution of the appropriate *N*-Boc indole (2.0 mmol) in THF (5 mL) at r.t. was added TBAF (8.0 mmol). The mixture was then heated under reflux for 10 h, and cooled at r.t. before addition of brine (10 mL), extraction with EtOAc (3 x 10 mL), and drying over Na_2SO_4. The solvents were removed under reduced pressure before purification by chromatography over silica gel (eluent given in the product description).

2-(4-Trifluoromethylphenyl)indole (24) was prepared from *N*-Boc 2-(4-trifluoromethylphenyl)indole (**2c**, 0.76 g).

Eluent: heptane/CH_2Cl_2 50/50.

Yield: 55% (0.29 g).

White powder.

Mp 228 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.93 (dd, 1H, *J* = 2.0, 1.0 Hz), 7.10-7.29 (m, 2H), 7.43 (d, 1H, *J* = 7.5 Hz), 7.62-7.81 (m, 5H), 8.39 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 101.5, 110.7, 110.8, 119.5, 120.2, 122.4, 123.9 (q, *J* = 226 Hz), 124.6 (2C), 125.3 (q, 2C, *J* = 4.1 Hz), 128.3 (q, *J* = 38 Hz), 135.5, 135.8, 137.4.

HRMS: calcd for $C_{15}H_{10}F_3N$ (M^+) 261.0765, found 261.0745.

These data were found identical to those previously described.[59]

2-(2-Pyridyl)indole (28) was prepared from *N*-Boc 2-(2-pyridyl)indole (**2e**, 0.60 g).

Eluent: CH_2Cl_2.

Yield: 67% (0.26 g).

Beige powder.

Mp 153 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, 1H, *J* = 1.5 Hz), 7.07-7.28 (m, 3H), 7.39 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.67 (dd, 1H, *J* = 7.5, 2.0 Hz), 7.75 (dd, 1H, *J* = 8.1, 2.0 Hz), 7.84 (td, 1H, *J* = 8.1, 1.5 Hz), 8.59 (m, 1H), 9.95 (s, 1H).

These data were found identical to those previously described.[60]

^{13}C NMR (75 MHz, $CDCl_3$): δ 100.6, 111.4, 119.8, 120.1, 121.1, 121.9, 123.1, 129.0, 136.5, 136.6, 136.7, 148.9, 150.3.

HRMS: calcd for $C_{13}H_{10}N_2$ (M^+) 194.0844, found 194.0851.

General Procedure for the Deprotection of *N*-Boc Indoles using TFA Followed by the Substitution of the Chloro Group with Amines (Compounds 29-47).

To a stirred solution of *N*-Boc 2-(2-chloro-4-pyrimidyl)indole (**2d**, 0.33 g, 1.0 mmol) in CH_2Cl_2 (5 mL) at r.t. was added TFA (15 mmol). After 2 h at r.t., a sat. aq $NaHCO_3$ solution (5 mL) was added. Extraction with EtOAc (3 x 5 mL), washing with brine (5 mL), drying over Na_2SO_4, and removal of the solvents under reduced pressure afforded crude 2-chloro-4-(2-indolyl)pyrimidine which was further dissolved in a mixture of pyridine (3 mL) and EtOH (3 mL). The required amine (3.0 mmol) was then added, and the reaction mixture was heated at 150 °C for 20 min in the microwave oven. After removal of the solvents under reduced pressure, the crude product was purified by MDAP.

4-(2-Indolyl)-*N*-propyl-2-pyrimidinamine (29) was prepared using *N*-propylamine (0.25 mL).

Yield: 44% (0.11 g).

Beige powder.

Mp 138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J* = 7.5 Hz), 1.68 (m, 2H), 3.47 (dt, 2H, *J* = 7.5, 4.4 Hz), 5.23 (s, 1H), 6.97 (d, 1H, *J* = 5.2 Hz), 7.09 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.12 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.43 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.29 (d, 1H, *J* = 5.2 Hz), 9.47 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 22.9, 43.4, 103.5, 105.7, 111.5, 120.4, 121.6, 124.1, 128.7, 135.0, 136.5, 157.4, 158.0, 162.3.

ESCI MS: *m/z* 253.19, $[M+H]^+$.

Anal. Calcd for $C_{15}H_{16}N_4$ (252.31): C, 71.40; H, 6.39; N, 22.21. Found: C, 71.33; H, 6.38; N, 22.26%.

4-(2-Indolyl)-*N*-isobutyl-2-pyrimidinamine (30) was prepared using isobutylamine (0.30 mL).

Yield: 48% (0.13 g).

Beige powder.

Mp 129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, 6H, *J* = 6.6 Hz), 1.94 (m, 1H), 3.34 (t, 2H, *J* = 6.6 Hz), 5.29 (s, 1H), 6.97 (d, 1H, *J* = 5.3 Hz), 7.10-7.16 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.42 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.49 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (2C), 28.5, 49.1, 103.5, 105.7, 111.5, 120.4, 121.6, 124.1, 128.7, 135.0, 136.5, 157.4, 158.0, 162.5.

ESCI MS: *m/z* 267.24, $[M+H]^+$.

Anal. Calcd for $C_{16}H_{18}N_4$ (266.34): C, 72.15; H, 6.81; N, 21.04. Found: C, 72.09; H, 6.80; N, 20.98%.

4-(2-Indolyl)-*N*-neopentyl-2-pyrimidinamine (31) was prepared using neopentylamine (0.35 mL).

Yield: 59% (0.17 g).

Pale yellow powder.

Mp 134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 9H), 3.36 (d, 2H, *J* = 6.1 Hz), 5.22 (s, 1H), 6.96 (d, 1H, *J* = 5.3 Hz), 7.09-7.16 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.44 (d, 1H, *J* = 8.3 Hz), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.27 (d, 1H, *J* = 5.3 Hz), 9.43 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5 (3C), 32.0, 52.8, 103.5, 105.7, 111.6, 120.4, 121.7, 124.1, 128.8, 135.0, 136.5, 157.4, 158.0, 162.8.

ESCI MS: *m/z* 281.03, $[M+H]^+$.

4-(2-Indolyl)-*N*-(2-trifluoromethylbenzyl)-2-pyrimidinamine (32) was prepared using 2-(trifluoromethyl)benzylamine (0.42 mL).

Yield: 45% (0.17 g).

Beige powder.

Mp 150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (d, 2H, *J* = 6.1 Hz), 5.69 (s, 1H), 7.05 (d, 1H, *J* = 5.0 Hz), 7.08-7.15 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.32-7.45 (m, 2H), 7.48 (ddd, 1H, *J* = 8.1, 7.9, 1.3 Hz), 7.60-7.73 (m, 3H), 8.29 (d, 1H, *J* = 5.0 Hz), 9.29 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 103.6, 106.4, 111.6, 120.5 (2C), 121.6, 123.9 (q, *J* = 225 Hz), 124.2, 126.2 (q, *J* = 3.6 Hz), 127.2, 128.8, 129.1 (q, *J* = 31 Hz), 132.2, 134.7, 136.5, 138.2, 157.4, 158.3, 161.9.

ESCI MS: *m/z* 368.99, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.23; H, 4.21; N, 15.28%.

4-(2-Indolyl)-*N*-(3-trifluoromethylbenzyl)-2-pyrimidinamine (33) was prepared using 3-(trifluoromethyl)benzylamine (0.43 mL).

Yield: 33% (0.12 g).

Beige powder.

Mp 157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, 2H, *J* = 6.1 Hz), 5.59 (s, 1H), 7.04 (d, 1H, *J* = 5.3 Hz), 7.10-7.16 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 0.9 Hz), 7.41 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.47 (t, 1H, *J* = 7.5 Hz), 7.54 (d, 1H, *J* = 7.5 Hz), 7.60 (d, 1H, *J* = 7.5 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 7.68 (s, 1H), 8.31 (d, 1H, *J* = 5.3 Hz), 9.24 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.5, 104.0, 106.8, 111.8, 120.7, 121.9, 124.3 (q, 2C, *J* = 3.7 Hz), 124.6 (q, *J* = 224 Hz), 124.6, 128.9, 129.4, 130.6 (q, *J* = 1.5 Hz), 130.9 (q, *J* = 32 Hz), 134.8, 136.8, 140.8, 157.7, 158.4, 162.3.

ESCI MS: *m/z* 369.04, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.01; H, 4.10; N, 15.11%.

4-(2-Indolyl)-*N*-(4-trifluoromethylbenzyl)-2-pyrimidinamine (34) was prepared using 4-(trifluoromethyl)benzylamine (0.43 mL).

Yield: 49% (0.18 g).

Beige powder.

Mp 131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, 2H, *J* = 6.1 Hz), 5.67 (s, 1H), 7.04 (d, 1H, *J* = 5.2 Hz), 7.10-7.16 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.39 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 7.60 (d, 2H, *J* = 8.1 Hz), 7.67 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.29 (d, 1H, *J* = 5.2 Hz), 9.33 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.3, 103.9, 106.7, 111.6, 120.7, 121.8, 124.1 (q, *J* = 273 Hz), 124.5, 125.6 (q, 2C, *J* = 3.7 Hz), 127.6 (2C), 128.8, 129.5 (q, *J* = 32 Hz), 134.7, 136.7, 143.7, 157.6, 158.3, 162.1.

ESCI MS: *m/z* 368.87, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.16; H, 4.18; N, 15.17%.

4-(2-Indolyl)-*N*-(2-methoxybenzyl)-2-pyrimidinamine (35) was prepared using 2-methoxybenzylamine (0.39 mL).

Yield: 50% (0.17 g).

Beige powder.

Mp 149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.73 (d, 2H, *J* = 6.1 Hz), 5.64 (s, 1H), 6.90-6.96 (m, 2H), 6.98 (d, 1H, *J* = 5.3 Hz), 7.09 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.12 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.23-7.30 (m, 2H), 7.38 (dd, 1H, *J* = 7.5, 1.3 Hz), 7.43 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1, 55.4, 103.4, 105.9, 110.4, 111.5, 120.4, 120.6, 121.6, 124.1, 127.3, 128.6, 128.8, 129.2, 135.0, 136.5, 157.3, 157.6, 158.1, 162.3.

ESCI MS: *m/z* 330.91, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.73; H, 5.57; N, 16.96%.

4-(2-Indolyl)-*N*-(3-methoxybenzyl)-2-pyrimidinamine (36) was prepared using 3-methoxybenzylamine (0.37 mL).

Yield: 43% (0.14 g).

White powder.

Mp 140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.70 (d, 2H, *J* = 5.7 Hz), 5.57 (s, 1H), 6.82 (ddd, 1H, *J* = 8.3, 2.6, 0.9 Hz), 6.95-7.02 (m, 2H), 7.00 (d, 1H, *J* = 5.3 Hz), 7.09-7.15 (m, 2H), 7.23-7.31 (m, 2H), 7.41 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.65 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.32 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.7, 55.2, 103.5, 106.2, 111.5, 112.6, 113.1, 119.6, 120.4, 121.6, 124.2, 128.7, 129.7, 134.8, 136.5, 141.1, 157.4, 158.2, 159.9, 162.1.

ESCI MS: *m/z* 330.91, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.77; H, 5.54; N, 17.04%.

4-(2-Indolyl)-*N*-(4-methoxybenzyl)-2-pyrimidinamine (37) was prepared using 4-methoxybenzylamine (0.39 mL).

Yield: 42% (0.14 g).

Beige powder.

Mp 161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 4.66 (d, 2H, *J* = 5.7 Hz), 5.44 (s, 1H), 6.89 (d, 2H, *J* = 8.8 Hz), 7.01 (d, 1H, *J* = 5.3 Hz), 7.10-7.15 (m, 2H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.33 (d, 2H, *J* = 8.8 Hz), 7.41 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.33 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 55.3, 103.5, 106.1, 111.5, 114.1 (2C), 120.4, 121.6, 124.2, 128.7, 128.8 (2C), 131.3, 134.9, 136.5, 157.4, 158.2, 158.9, 162.1.

ESCI MS: *m/z* 330.91, $[M+H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.65; H, 5.47; N, 16.87%.

***N*-(2-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (38)** was prepared using 2-chlorobenzylamine (0.36 mL).

Yield: 36% (0.12 g).

White powder.

Mp 153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (d, 2H, *J* = 6.1 Hz), 5.66 (s, 1H), 7.01 (d, 1H, *J* = 5.1 Hz), 7.10 (dd, 1H, *J* = 1.7, 0.9 Hz), 7.12 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.20-7.29 (m, 3H), 7.38-7.50 (m, 3H), 7.65 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.29 (d, 1H, *J* = 5.1 Hz), 9.38 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 43.5, 103.8, 106.6, 111.8, 120.7, 121.9, 124.4, 127.2, 128.8, 128.9, 129.5, 129.8, 133.6, 135.0, 136.8, 137.0, 157.7, 158.4, 162.3.

ESCI MS: *m/z* 334.91, 336.85 $[M+H]^+$.

Anal. Calcd for $C_{19}H_{15}ClN_4$ (334.80): C, 68.16; H, 4.52; N, 16.73. Found: C, 68.12; H, 4.62; N, 16.58%.

***N*-(3-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (39)** was prepared using 3-chlorobenzylamine (0.37 mL).

Yield: 10% (33 mg).

White powder.

Mp 160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (d, 2H, *J* = 5.8 Hz), 5.57 (s, 1H), 7.02 (d, 1H, *J* = 5.3 Hz), 7.11 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.24-7.33 (m, 4H), 7.41-7.43 (m, 2H), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.30 (d, 1H, *J* = 5.3 Hz), 9.24 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 103.8, 106.6, 111.7, 120.6, 121.8, 124.3, 125.5, 127.5 (2C), 128.8, 130.0, 134.6, 134.8, 136.6, 141.7, 157.6, 158.3, 162.1.

ESCI MS: *m/z* 334.99, 336.97 $[M+H]^+$.

***N*-(4-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (40)** was prepared using 4-chlorobenzylamine (0.37 mL).

Yield: 12% (40 mg).

Beige powder.

Mp 162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (d, 2H, *J* = 6.1 Hz), 5.51 (s, 1H), 7.03 (d, 1H, *J* = 5.3 Hz), 7.12 (dd, 1H, *J* = 2.1, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.30-7.36 (m, 4H), 7.41 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.29 (d, 1H, *J* = 5.3 Hz), 9.27 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 104.0, 106.7, 111.8, 120.7, 121.9, 124.5, 128.9, 129.0 (2C), 129.1 (2C), 133.2, 134.9, 136.8, 138.1, 157.7, 158.4, 162.3.

ESCI MS: *m/z* 335.03, 337.02 $[M+H]^+$.

***N*-(2-Fluorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (41)** was prepared using 2-fluorobenzylamine (0.34 mL).

Yield: 41% (0.13 g).

White powder.

Mp 146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (d, 2H, *J* = 6.1 Hz), 5.71 (s, 1H), 7.01 (d, 1H, *J* = 5.3 Hz), 7.05-7.15 (m, 4H), 7.22-7.29 (m, 2H), 7.40-7.47 (m, 2H), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.45 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 103.8, 106.5, 111.8, 115.3 (d, *J* = 21 Hz), 120.6, 121.9, 124.4, 124.5 (d, *J* = 3.7 Hz), 126.3 (d, *J* = 15 Hz), 129.0 (d, *J* = 8.1 Hz), 129.2, 129.9 (d, *J* = 4.4 Hz), 135.0, 136.8, 157.6, 158.4, 161.0 (d, *J* = 245 Hz), 162.3.

ESCI MS: *m/z* 318.86, $[M+H]^+$.

Anal. Calcd for $C_{19}H_{15}FN_4$ (318.35): C, 71.68; H, 4.75; N, 17.60. Found: C, 71.52; H, 4.83; N, 17.58%.

4-(2-Indolyl)-*N*-(4-*tert*-butylbenzyl)-2-pyrimidinamine (42) was prepared using 4-*tert*-butylbenzylamine (0.53 mL).

Yield: 43% (0.15 g).

White powder.

Mp 162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 4.71 (d, 2H, *J* = 5.7 Hz), 5.54 (s, 1H), 7.01 (d, 1H, *J* = 5.3 Hz), 7.11 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.33-7.44 (m, 5H), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.34 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 31.6 (3C), 34.7, 45.6, 103.7, 106.3, 111.8, 120.6, 121.7, 124.4, 125.8 (2C), 127.4 (2C), 128.9, 135.1, 136.5, 136.7, 150.6, 157.6, 158.4, 162.4.

Anal. Calcd for $C_{23}H_{24}N_4$ (356.46): C, 77.50; H, 6.79; N, 15.72. Found: C, 77.62; H, 6.97; N, 15.29%.

4-(2-Indolyl)-*N*-(3,4,5-trimethoxybenzyl)-2-pyrimidinamine (43) was prepared using 3,4,5-trimethoxybenzylamine (0.51 mL).

Yield: 37% (0.14 g).

Beige powder.

Mp 143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.84 (s, 3H), 4.65 (d, 2H, *J* = 5.7 Hz), 5.65 (s, 1H), 6.62 (s, 2H), 7.02 (d, 1H, *J* = 5.3 Hz), 7.10-7.15 (m, 2H), 7.25 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.39 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.29 (d, 1H, *J* = 5.3 Hz), 9.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 56.3 (2C), 61.1, 103.9, 104.5 (2C), 106.5, 111.7, 120.7, 121.9, 124.5, 128.7, 134.7, 135.0, 136.6, 137.1, 153.4 (2C), 157.5, 158.1, 162.1.

ESCI MS: *m/z* 391.04, $[M+H]^+$.

Anal. Calcd for $C_{22}H_{22}N_4O_3$ (390.44): C, 67.68; H, 5.68; N, 14.35. Found: C, 67.51; H, 5.72; N, 14.01%.

4-(2-Indolyl)-*N*-(2-pyridylmethyl)-2-pyrimidinamine (44) was prepared using 2-(aminomethyl)pyridine (0.31 mL).

Yield: 73% (0.22 g).

Beige powder.

Mp 178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (d, 2H, *J* = 5.7 Hz), 6.22 (s, 1H), 7.01 (d, 1H, *J* = 5.1 Hz), 7.09 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.11 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.17-7.22 (m, 1H), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.37 (d, 1H, *J* = 7.9 Hz), 7.43 (ddd, 1H, *J* = 8.3, 1.7, 0.9 Hz), 7.63-7.68 (m, 2H), 8.31 (d, 1H, *J* = 5.1 Hz), 8.61 (ddd, 1H, *J* = 4.8, 1.8, 0.9 Hz), 9.49 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 47.2, 103.7, 106.4, 111.8, 120.6, 121.7, 121.8, 122.4, 124.4, 128.9, 135.1, 136.8, 136.9, 149.3, 157.6, 158.3, 158.4, 162.3.

ESCI MS: *m/z* 302.05, $[M+H]^+$.

Anal. Calcd for $C_{18}H_{15}N_5$ (301.35): C, 71.74; H, 5.02; N, 23.24. Found: C, 71.48; H, 4.98; N, 23.26%.

***N*-(3-Furylmethyl)-4-(2-indolyl)-2-pyrimidinamine (45)** was prepared using 3-furylmethylamine (0.26 mL).

Yield: 65% (0.19 g).

Pale brown powder.

Mp 144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (d, 2H, *J* = 5.7 Hz), 5.53 (s, 1H), 6.27-6.36 (m, 2H), 7.03 (d, 1H, *J* = 5.3 Hz), 7.12 (dd, 1H, *J* = 2.2, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.27 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.38 (dd, 1H, *J* = 1.8, 0.9 Hz), 7.43 (ddd, 1H, *J* = 8.3, 1.7, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.30 (d, 1H, *J* = 5.3 Hz), 9.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 39.1, 103.8, 106.6, 107.1, 110.7, 111.8, 120.7, 121.9, 124.5, 128.9, 135.0, 136.8, 142.2, 152.8, 157.6, 158.3, 162.1.

ESCI MS: *m/z* 291.05, $[M+H]^+$.

***N*-Cyclohexyl-4-(2-indolyl)-2-pyrimidinamine (46)** was prepared using cyclohexylamine (0.34 mL).

Yield: 70% (0.20 g).

Pale yellow powder.

Mp 114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.35 (m, 2H), 1.39-1.53 (m, 2H), 1.60-1.72 (m, 2H), 1.73-1.84 (m, 2H), 2.01-2.14 (m, 2H), 3.87-4.00 (m, 1H), 5.08 (d, 1H, *J* = 7.9 Hz), 6.95 (d, 1H, *J* = 5.3 Hz), 7.10 (dd, 1H, *J* = 1.8, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 0.9 Hz), 7.26 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.43 (dd, 1H, *J* = 8.3, 0.9 Hz), 7.66 (dd, 1H, *J* = 7.9, 1.3 Hz), 8.27 (d, 1H, *J* = 5.3 Hz), 9.36 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (2C), 26.0, 33.5 (2C), 49.9, 103.7, 105.8, 111.7, 120.6, 121.8, 124.3, 129.0, 135.2, 136.7, 157.6, 158.3, 161.8.

ESCI MS: *m/z* 292.89, $[M+H]^+$.

4-(2-Indolyl)-*N*-(*N*-methyl-4-piperidyl)-2-pyrimidinamine (47) was prepared using 4-amino-*N*-methylpiperidine (0.34 g).

Yield: 50% (0.15 g).

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-1.71 (m, 2H), 2.07-2.16 (m, 2H), 2.23 (t, 2H, *J* = 11 Hz), 2.33 (s, 3H), 2.82 (d, 2H, *J* = 11 Hz), 3.95 (m, 1H), 5.06 (d, 1H, *J* = 7.9 Hz), 6.98 (d, 1H, *J* = 5.3 Hz),

7.11 (dd, 1H, *J* = 1.8, 0.9 Hz), 7.13 (ddd, 1H, *J* = 7.9, 7.0, 1.3 Hz), 7.26 (ddd, 1H, *J* = 8.1, 7.0, 0.9 Hz), 7.43 (d, 1H, *J* = 8.1 Hz), 7.66 (dd, 1H, *J* = 7.9, 0.9 Hz), 8.28 (d, 1H, *J* = 5.3 Hz), 9.36 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 32.6 (2C), 46.5, 47.6, 54.7 (2C), 103.8, 106.1, 111.8, 120.7, 121.9, 124.4, 130.0, 135.1, 136.7, 157.7, 158.3, 161.9.

ESCI MS: *m/z* 292.89, $[M+H]^+$.

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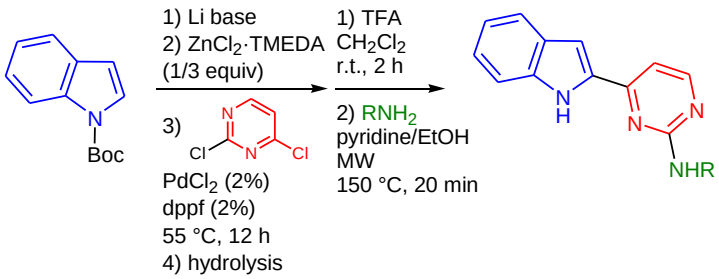
Graphical abstract:



Short title:

Cross-couplings of lithium arylzincates/Synthesis of Isomeridianine G analogues